Enclosure A

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

PUREPAC PHARMACEUTICAL CO.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Case No. 03-2210 (TPJ)
	)	
TOMMY G. THOMPSON, Secretary of Health and Human Services, and MARK B. McCLELLAN, Commissioner of Food and Drugs,	)	
	)	
Defendants,	)	
	)	
and	)	
	)	
IVAX PHARMACEUTICALS, INC.,	)	
	)	
Intervenor-Defendant.	)	
	)	

FEDERAL DEFENDANTS' MEMORANDUM IN OPPOSITION TO PLAINTIFF'S MOTION FOR PRELIMINARY INJUNCTION

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INTRODUCTION

Plaintiff Purepac Pharmaceutical Co. ("Purepac") challenges a decision of the Food and Drug Administration ("FDA") regarding the approval of a generic version of metformin hydrochloride extended-release tablets 500 mg ("metformin") under the provisions of the Federal Food, Drug and Cosmetic Act (the "FDCA" or "Act") pertaining to drug approvals (the "Hatch-Waxman Amendments"). 21 U.S.C. §§ 355, 360cc, and 35 U.S.C. §§ 156, 271, 282. Purepac and a competing generic drug manufacturer, Intervenor-Defendant IVAX Pharmaceuticals, Inc. ("IVAX"), each submitted an abbreviated new drug application ("ANDA") for metformin. On October 28, 2003, FDA approved IVAX's ANDA and determined that Purepac's ANDA would not be eligible for final approval until after the expiration of a 180-day period of marketing exclusivity to which IVAX was entitled. After a hearing on Purepac's motion for a temporary restraining order on October 29, 2003, and Purepac's posting a required bond on October 30, 2003, FDA suspended IVAX's approval on October 30, 2003, pursuant to this Court's order. Purepac contends that it, not IVAX, is entitled to 180-day exclusivity for metformin and that approval of IVAX's ANDA should await the expiration of Purepac's exclusivity period.

Purepac's claim to exclusivity rests on U.S. Patent Number 6,475,521 ("the '521 patent") submitted to FDA by Bristol Myers Squibb ("BMS") on November 20, 2002. Purepac submitted an amendment to its ANDA containing a so-called "paragraph IV" certification to the '521 patent on the same day, but, contrary to the statutory requirements, waited one week, until November 27, 2002, to provide notice to BMS. In the meantime, one day earlier, on November 26, 2002, IVAX submitted an original ANDA with a paragraph IV certification to the '521 patent. FDA determined that, consistent with its expressed interpretation of the FDCA and FDA regulations, IVAX had submitted the "first" effective paragraph IV certification. An original ANDA which includes a paragraph IV certification is considered effectively submitted on the date it is received

by FDA, provided that FDA finds, after conducting a threshold review, that the application is substantially complete. A paragraph IV certification contained in an ANDA amendment, however, is not considered effectively submitted until it has both been received by FDA and the ANDA applicant has provided notice to the NDA holder and patent owner. Because the receipt date of IVAX's ANDA preceded the latter of the two dates by which FDA had received Purepac's paragraph IV certification and Purepac had provided notice, IVAX was the first ANDA applicant to meet the statutory requirements. FDA therefore concluded that IVAX is entitled to exclusivity on the '521 patent.

Purepac now seeks preliminary and permanent injunctive relief against the Secretary of Health and Human Services and the FDA Commissioner (collectively "FDA" or "federal defendants") to compel FDA to reverse course and award 180-day exclusivity for metformin to Purepac and to delay final approval of IVAX's ANDA (and all other metformin ANDAs) until Purepac's 180-day exclusivity has run. Purepac asserts that it was first to submit its paragraph IV certification and first to provide notice, and contends that it is therefore entitled exclusivity regardless of whether the date of certification or the date of notice controls.

Although this argument has surface appeal, it ignores the fact that the statute has different requirements for the timing of notice depending on whether a paragraph IV certification is contained in an original ANDA (as IVAX's was) or an ANDA amendment (as Purepac's was). FDA properly treats these types of submission differently because: (1) the plain language of the statute contains different notice requirements for the two submissions; (2) the implementing regulations contain different notice requirements for the two submissions; and (3) there are policy reasons, relating to the purposes of the Hatch-Waxman Amendments, as to why these submissions should be treated differently. Because of these differences, FDA has reasonably

determined that notice is a necessary prerequisite for effective submission of an ANDA amendment containing a paragraph IV certification, while the submission of an original ANDA with a paragraph IV certification is effective on the date of receipt regardless of the date notice is provided.

Purepac is therefore not entitled to the relief it seeks. In awarding exclusivity to IVAX's ANDA, FDA correctly applied the statutory and regulatory requirements governing ANDA approvals and 180-day exclusivity. Because the agency's action was not arbitrary, capricious, an abuse of discretion, or otherwise contrary to law, Purepac has no likelihood of success on the merits. Moreover, Purepac has not demonstrated that it will suffer irreparable injury absent injunctive relief or that the request relief is in the public interest. Unlike IVAX, which has demonstrated that it is ready and able to market its generic metformin product, there is nothing of record indicating that Purepac will obtain FDA approval of its ANDA and be in a position to launch its generic metformin drug in the near future. Entry of the requested preliminary injunction is thus contrary to the public interest as it will delay generic competition for metformin and deprive consumers of a lower cost alternative to the brand-name product. For these reason, Purepac's motion for preliminary injunction should be denied.

STATUTORY AND REGULATORY FRAMEWORK

A. New Drug Applications

Under the FDCA, pharmaceutical companies seeking to market "pioneer" or "innovator" drugs must first obtain FDA approval by filing a new drug application ("NDA") containing extensive scientific data demonstrating the safety and effectiveness of the drug. 21 U.S.C. §§ 355(a), (b). An NDA applicant must also submit information on any patent that claims the drug or a method of using the drug and for which a claim of patent infringement could

reasonably be asserted against an unauthorized party. 21 U.S.C. §§ 355(b)(1), (c)(2). FDA is required to publish the patent information it receives, and does so, in the "Approved Drug Products With Therapeutic Equivalence Evaluations" (the "Orange Book"). Id.; see also 21 C.F.R. § 314.53(e).

B. Abbreviated New Drug Applications

The Hatch-Waxman Amendments to the FDCA permit the submission of ANDAs for approval of generic versions of approved drug products. 21 U.S.C. § 355(j). Under the abbreviated procedure, ANDA applicants may rely upon FDA findings of safety and effectiveness for pioneer drugs. 21 U.S.C. § 355(j)(2). The timing of approval of ANDAs depends in part on patent protections for the pioneer drug. The FDCA sets forth in detail the information that an ANDA must contain. See 21 U.S.C. § 355(j)(2).

1. Patent Certifications

Among other things, the ANDA must contain one of four specified certifications for each patent that "claims the listed drug" or "a use for such listed drug for which the applicant is seeking approval." 21 U.S.C. § 355(j)(2)(A)(vii). FDA has defined the "listed drug" to mean the approved new "drug product." 21 C.F.R. § 314.3(b). This certification must state one of the following:

> (I) that the required patent information relating to such patent has not been filed;
>
> (II) that such patent has expired;
>
> (III) that the patent will expire on a particular date; or
>
> (IV) that such patent is invalid or will not be infringed by the drug for which approval is being sought.

See 21 U.S.C. § 355(j)(2)(A)(vii). If a certification is made under paragraph I or II indicating

that patent information pertaining to the drug or its use has not been filed with FDA or the patent has expired, the ANDA may be approved immediately. 21 U.S.C. § 355(j)(5)(B)(i). A certification under paragraph III indicates that the ANDA applicant does not intend to market the drug until after the applicable patent expires, and approval of the ANDA may be made effective on the expiration date. 21 U.S.C. § 355(j)(5)(B)(ii).

If an applicant wishes to challenge the validity of the patent, or to claim that the patent would not be infringed by the product proposed in the ANDA, the applicant must submit a paragraph IV certification to FDA. The applicant must also provide a notice to the NDA holder and the patent owner stating that the application with a paragraph IV certification has been submitted and explaining the factual and legal basis for the applicant's opinion that the patent is invalid or not infringed. 21 U.S.C. § 355(j)(2)(B). The filing of a paragraph IV certification "for a drug claimed in a patent or the use of which is claimed in a patent" is an act of infringement, 35 U.S.C. § 271(e)(2)(A), thus enabling the NDA holder and patent holder to sue the ANDA applicant. If the patent holder or NDA holder brings a patent infringement suit against the ANDA applicant within 45 days of the date it receives notice of the paragraph IV certification, FDA will stay approval of the ANDA for 30 months from the date that the patent owner and NDA holder received notice, unless a final court decision is reached earlier in the patent case or the patent court otherwise orders a longer or shorter period. 21 U.S.C. § 355(j)(5)(B)(iii). If no action is brought within 45 days, FDA may approve an ANDA with a paragraph IV certification, and the approval may become effective immediately despite the unexpired patent, provided that other conditions for approval are met. 21 U.S.C. § 355(j)(5)(B)(iii); 21 C.F.R. § 314.107(f)(2).

2. Notice of Paragraph IV Certifications

An ANDA applicant who submits a paragraph IV certification must notify the patent owner and the NDA holder for the listed drug. 21 U.S.C. § 355(j)(2)(B). This notice must include a detailed statement of the factual and legal basis for the ANDA applicant's opinion that the patent is not valid or will not be infringed by the drug product for which approval is sought. 21 U.S.C. § 355(j)(2)(B)(ii); 21 C.F.R. § 314.95(c).

The timing of notice differs depending on whether a paragraph IV certification is contained in an original ANDA or an ANDA amendment. FDA will not accept an original ANDA until it has made a threshold determination that the application is sufficiently complete to permit substantive review. 21 C.F.R. § 314.101(b). Once FDA determines that the application is sufficiently complete to permit substantive review, FDA considers the ANDA to have been effectively submitted on the date the substantially complete application was received and date-stamped by the appropriate FDA document room, not the date that FDA completes its threshold review. See id.; see also 21 C.F.R. § 314.101(f)(2) (FDA measures its deadline (180 days) for approving or disapproving ANDA from initial ANDA receipt date, not date FDA completes threshold review); 54 Fed. Reg 28872, 28889 (July 10, 1989) (same); Notice of Availability: Guidance for Industry on 180-Day Exclusivity When Multiple Abbreviated New Drug Applications Are Submitted on the Same Day ("Guidance"), 68 Fed. Reg. 45252, 45254 (Aug. 1, 2003) ("CDER considers most documents . . . . to have been submitted to FDA as the date stamped on the document by the appropriate CDER document room"). See, e.g., Administrative Record ("AR"), Tab 8 ("DATE (RECEIVED) ACCEPTABLE FOR FILING: November 26, 2002").

After FDA has accepted the ANDA for filing, the ANDA applicant must then give notice of any paragraph IV certifications to the patent owner and NDA holder. The statute provides that an applicant submitting a paragraph IV certification with an original ANDA "shall include in the application a statement that the applicant will give the notice required by clause (ii) . . . ." 21 U.S.C. § 355(j)(2)(B)(i) (emphasis added). Under FDA's regulations, notice of a paragraph IV certification contained in an original ANDA is to be provided when the ANDA applicant has received acknowledgment from FDA that the ANDA has been received and is sufficiently complete to permit a substantive review. See 21 C.F.R. § 314.95(b). If, instead, ANDA applicants were to provide notice of paragraph IV certifications at the time of the original submission of the ANDA, they would be giving notice of such certifications before FDA had decided whether to accept or reject the ANDA for filing. Such notice could thus generate unnecessary patent litigation over an ANDA that might never be filed or reviewed by FDA. As FDA explained in proposing this regulation:

> [Under this regulation], an applicant is required to provide the notice of certification when it receives FDA's acknowledgment of the receipt of an ANDA that is acceptable for review. Although the legislative history states that Congress intended that the notice be sent simultaneously with submission to FDA of the ANDA, the statute requires the applicant to state in the notice that an application "has been submitted." Moreover, the statute requires the notice to state that the application contains data from bioavailability or bioequivalence studies. Receipt of the notice by the patent owner or its representative or the approved application holder triggers the start of the 45-day clock within which a patent owner or application holder must bring suit if it wishes to challenge an applicant's certification of patent invalidity or noninfringement. The statute and legislative history of Title I demonstrate that Congress did not intend incomplete application submissions to trigger legal action by a patent owner or approved application holder.
>
> The agency therefore proposes that the notice be sent only upon submission of a "complete" application. An applicant must first submit an ANDA and certify in the application that it will provide the required notice to the patent owner or its representative and to the pioneer application holder. After receipt of the application, the agency will determine if the application is acceptable for review.

54 Fed. Reg. at 28887.

The statutory and regulatory requirements for an ANDA that is amended to include a paragraph IV certification are different. The statute provides that "the notice required by clause (ii) shall be given when the amended application is submitted." 21 U.S.C. § 355(j)(2)(B)(iii) (emphasis added). FDA regulations implement the statutory language by requiring an applicant amending an ANDA to include a paragraph IV certification to send the required notice "at the same time" it submits the amendment to FDA. 21 C.F.R. § 314.95(d). These provisions mean that an ANDA amendment containing a paragraph IV certification is not effectively submitted to FDA until the ANDA amendment is received by FDA and the ANDA applicant provides the required notice to the patent owner and NDA holder. AR, Tab 15 (Letter to Apotex Corp. and Purepac from FDA's Office of Generic Drugs re: 180-day Exclusivity) (Jan. 28, 2003). That interpretation has been upheld by Judge Huvelle of this Court. TorPharm, Inc. v. Thompson, 260 F. Supp. 2d 69, 71, 79-81 (D.D.C. 2003), appeal pending, No. 02-5410 (D.C. Cir.) (oral argument scheduled for November 25, 2003).

3. 180-Day Period Of Market Exclusivity

As an incentive to the first generic drug manufacturer to expose itself to the risk of patent litigation, the statute provides that the first manufacturer who submits an ANDA containing a paragraph IV certification is eligible for a 180-day period of marketing exclusivity. 21 U.S.C. § 355(j)(5)(B)(iv). See Mova Pharm. Corp. v. Shalala, 140 F.3d 1060, 1064 (D.C. Cir. 1998). The statutory provision governing 180-day exclusivity provides:

> If the application contains a certification described in subclause IV of paragraph (2)(A)(vii) and is for a drug for which a previous application has been submitted under this subsection [containing] such a certification, the application shall be made effective not earlier than one hundred and eighty days after-

(I) the date the Secretary receives notice from the applicant under the previous application of the first commercial marketing of the drug under the previous application, or

(II) the date of a decision of a court in an action described in clause (iii) holding the patent which is the subject of the certification to be invalid or not infringed,

whichever is earlier.

21 U.S.C. § 355(j)(5)(B)(iv).

If there is one "first" ANDA entitled to exclusivity, no other ANDA for that drug product can be approved until the 180-day period expires. The rules for determining the effective date for submissions of paragraph IV certifications discussed in the preceding section govern the determination of who is "first" for 180-day exclusivity purposes. See AR, Tab 15 at 6-7. The exclusivity can be triggered by either the first commercial marketing under the ANDA entitled to exclusivity or by a decision of a court finding the patent covering the innovator drug invalid, unenforceable, or not infringed, whichever occurs first. 21 U.S.C. § 355(j)(5)(B)(iv); 21 C.F.R. § 314.107(c).

FACTUAL BACKGROUND

BMS holds the NDA for metformin, which it markets under the name Glucophage-XR Extended Release Tablets and which is used by diabetics for blood sugar control. BMS submitted the '521 patent to FDA for listing in connection with its metformin NDA on November 20, 2002. AR, Tab 1.[1]

[1] Patent information is considered submitted on the date it is received by FDA's Central Document Room. 21 C.F.R. § 314.53(d)(5).

FDA received Purepac's ANDA for metformin on July 1, 2002. AR, Tab 2.[2] The United States Patent Office issued the '521 patent to BMS on November 5, 2002. Purepac's Statement of Material Facts ¶ 4. Purepac immediately began submitting to FDA ANDA amendments containing a paragraph IV certification to the '521 patent, and continued to do so every business day until FDA's receipt of BMS's patent submission was posted on the Internet. See AR, Tab 4. FDA received these paragraph IV submissions daily from November 6 to November 26, 2002. (Purepac faxed copies of these submissions as well, from November 5 to November 25, but FDA does not recognize paragraph IV certifications sent in by fax. See Guidance, 68 Fed. Reg. at 45254 n.4.). Because an ANDA applicant cannot certify to a patent before it has been listed, Purepac's ANDA amendments received by FDA before its receipt of the patent information were premature and considered by the agency to be null and void. However, one of Purepac's ANDA amendments was received by FDA on November 20, 2002, the date the '521 patent was listed, and was therefore properly submitted. Purepac sent notice of its paragraph IV certification to BMS on November 27, 2002. AR, Tab 5. BMS did not file suit against Purepac on that patent.

IVAX submitted an original ANDA for metformin on November 26, 2002. AR, Tab 7. IVAX included in its ANDA a paragraph IV certification to the '521 patent. Id. On January 14, 2003, FDA issued an acknowledgment letter to IVAX stating that the application was received as of November 26, 2002. AR, Tab 8. The letter explained that the applicant must comply with the notice requirements contained in the statute, and provide documentation of such notice to

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[2] The effective date of the submission of an original ANDA or ANDA amendment is determined, in part, by the date of FDA's receipt, as opposed to the date of mailing by the applicant. See Guidance, 68 Fed. Reg. at 45254. This practice was upheld in TorPharm, 260 F. Supp. 2d at 81-82. The court found that it was "well within the FDA's administrative discretion to adopt this sort of reasonable 'housekeeping' rule to make it easier for the agency to determine the order in which amended paragraph IV certifications are filed." Id. at 82.

FDA. Id. FDA sent its January 14, 2003, letter to IVAX by regular mail, and has no information on when it was received.[3] IVAX sent notice to BMS on February 3, 2003. AR, Tab 10. BMS did not file suit against IVAX on that patent.

On October 28, 2003, FDA approved IVAX's ANDA. AR, Tab 12. FDA explained in the approval letter that it had determined that IVAX was the first ANDA applicant to effectively submit a paragraph IV certification to the '521 patent. Id. Therefore, IVAX was entitled to 180-day exclusivity for metformin. Id.

On October 29, 2003, Purepac filed this lawsuit. The Court entered a temporary restraining order ("TRO") the same day. On October 30, 2003, pursuant to the Court's order, FDA suspended approval of IVAX's metformin ANDA. AR, Tab 14.

ARGUMENT

FDA properly determined that IVAX, not Purepac, is entitled to exclusivity on the '521 patent. FDA has established rules to determine who is the "first" ANDA applicant eligible for exclusivity on a particular patent, and these rules apply to all ANDA applicants. The rules are based upon the language of the statute, and are reflected in FDA regulations and long-standing policy. Under these rules, an applicant submitting an original ANDA containing a paragraph IV certification is not required to provide simultaneous notice to the patent holder and NDA holder; the statute requires instead that the applicant file a statement that it "will give" notice. Notice at the time of the original ANDA submission would be premature, because FDA would not yet have determined whether the ANDA is acceptable for filing, and the giving of notice could

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[3] Federal defendants note that FDA sent Purepac its original ANDA acknowledgment letter on August 27, 2002, AR Tab 3, which Purepac claims to have received on September 4, 2002 – some eight days later. Purepac's Statement of Material Facts ¶ 3. Assuming a similar time-lag in the delivery of IVAX's acknowledgment letter, it is reasonable to assume that IVAX received FDA's letter on or about January 22, 2003.

engender unnecessary patent litigation. Indeed, given that the patent owner and NDA holder have 45 days from the date of notice to file suit, but FDA may take more than 45 days to conduct its threshold review, in most cases patent litigation could begin before FDA has decided whether to receive the ANDA for filing. Once FDA makes that threshold determination, however, the effective ANDA submission date relates back to the original submission date.

By contrast, the statute and regulations explicitly require that an ANDA applicant who submits to FDA an ANDA amendment with a paragraph IV certification give notice of that certification to the patent owner and NDA holder simultaneously with the submission of the amendment. Unlike the situation with an original ANDA, there is no reason for notice to be delayed when a paragraph IV certification is submitted after the ANDA has already been received for filing because any potential patent dispute would be immediately ripe. Further, an applicant submitting an original ANDA must wait for FDA to conduct its initial review before giving notice; any delay in notice by an applicant submitting an ANDA amendment is only attributable to the applicant itself.

Although the statute does not itself specify the consequences of an applicant's failure to comply with the requirement of simultaneous notice, FDA has filled this gap by reasonably construing the statute and its regulations to require two acts to make an ANDA amendment containing a paragraph IV certification effective for exclusivity purposes: (1) submission of the certification to FDA, and (2) notice to the patent owner and NDA holder. The record demonstrates that Purepac completed these two acts after IVAX submitted its substantially complete ANDA containing a paragraph IV certification. Under the straightforward application of the statute described above, IVAX is entitled to 180-day exclusivity. Although Purepac views the application of these rules to the facts of this case as unfair, FDA applies these rules to

everyone. Indeed, had Purepac complied with the clear statutory and regulatory command by sending notice to BMS at the same time it filed its ANDA amendment, it would have been entitled to exclusivity instead of IVAX. Having failed to do so, however, Purepac is in no position to cry foul.[4]

Nor can it be claimed that requiring both the notice and certification requirements to be fulfilled before an ANDA amendment will be considered effectively submitted somehow imposes new or additional conditions as prerequisites to obtaining exclusivity. To the contrary, FDA's refusal to consider Purepac's ANDA amendment "submitted" until the requisite notice was given reflects, as Judge Huvelle recognized in TorPharm, a reasonable and permissible exercise of the agency's broad discretion. FDA's decision ensures that Congress' will is not thwarted, while striking a sensible balance between competing interests – neither rewarding Purepac for prematurely submitting its paragraph IV certification without providing the required simultaneous notice, nor unduly penalizing it by voiding its ANDA submission altogether. Because FDA has thus permissibly construed the relevant statutory provisions to establish a set of rules applicable to all ANDA applicants, and has properly applied those rules to this case, its determination should be upheld.

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[4] Purepac not only failed to comply with the statutory requirement of simultaneous notice with respect to its November 21, 2002, certification, but also improperly submitted to FDA a series of certifications before the '521 patent was submitted to FDA. Purepac's decision to bombard FDA with premature ANDA amendments in order to gain an advantage over other ANDA applicants can only be characterized as an attempt to "game" the system. In any event, assuming Purepac had a good faith basis for believing the '521 patent was invalid or would not be infringed by its product from the moment of the patent issued, there is reason to question the company's failure to detail the factual and legal basis for its belief in the required notice and send it to the patent owner and NDA holder simultaneously with its ANDA submissions. Given Purepac's willingness to exploit the statutory certification process for competitive advantage, it is hardly unfair to demand that Purepac fully comply with the statutory requirements in order to earn the reward it so eagerly sought.

Moreover, Purepac has failed to demonstrate the other elements necessary for a preliminary injunction. Purepac has demonstrated nothing other than monetary harm to itself from denial of the injunction and has not shown, or even alleged, that the economic harm it envisions would be so severe as cause extreme hardship to, or threaten destruction of, its business. Conversely, entry of the injunction is clearly contrary to the public interest because it will delay the entry of a generic metformin to the market and deprive American consumers of a lower cost alternative to BMS' brand-name Glucophage XR product. For all of these reasons, Purepac's motion for a preliminary injunction should be denied.

STANDARD OF REVIEW

To obtain preliminary injunctive relief, Purepac must demonstrate that: (1) it has a substantial likelihood of success on the merits; (2) it will suffer irreparable injury in the absence of preliminary relief; (3) other interested parties will not be substantially injured if the requested relief is granted; and (4) granting such relief would serve the public interest. E.g., Mova Pharm. Corp. v. Shalala, 140 F.3d 1060, 1066 (D.C. Cir. 1998). The Court must balance the four factors in deciding whether to grant the injunctive relief. Id. (citing CityFed Fin. Corp. v. Office of Thrift Supervision, 58 F.3d 738, 747 (D.C. Cir. 1995)).

A preliminary injunction is "an extraordinary form of judicial relief" and is not to be granted lightly. Mylan Pharm., Inc. v. Thompson, 139 F. Supp. 2d 1, 17 (D.D.C.), rev'd other grounds, 268 F.3d 1323 (Fed. Cir. 2001), cert. denied, 537 U.S. 941 (2002); Bristol-Myers Squibb Co. v. Shalala, 923 F. Supp. 212, 215 (D.D.C. 1996) (citing WMATC v. Holiday Tours, Inc., 559 F.2d 841, 843 (D.C. Cir. 1977)). Moreover, although Purepac's preliminary injunction motion itself seeks only to maintain the temporary suspension of IVAX's ANDA approval pending resolution of the merits, the ultimate relief Purepac seeks – an order compelling FDA to

grant Purepac exclusivity on its metformin ANDA – is a "mandatory injunction" that must be reviewed "with even greater circumspection." Mylan Pharm., Inc. v. Shalala, 81 F. Supp. 2d 30, 36 (D.D.C. 2000). Because Purepac has failed to meet the stringent standards for such extraordinary relief, its motion for a preliminary injunction should be denied.

I. PUREPAC HAS NO LIKELIHOOD OF SUCCESS ON THE MERITS

A. FDA's Administrative Determinations are Entitled to Deference

FDA's actions in this case are subject to review by the Court under the Administrative Procedure Act ("APA"), and may be disturbed only if "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A); Sultan Chemists, Inc. v. EPA, 281 F.3d 73, 78-79 (3d Cir. 2002). This standard is highly deferential to the agency. Citizens to Preserve Overton Park, Inc. v. Volpe, 401 U.S. 402, 416 (1971). Indeed, "[t]here is a presumption in favor of the validity of the administrative action." Bristol-Myers, 923 F. Supp. at 216 (citing Ethicon, Inc. v. FDA, 762 F. Supp. 382 (D.D.C. 1991)); see also Watson v. Henney, 194 F. Supp. 2d at 442, 445. The reviewing court must consider whether the agency's decision was based upon a consideration of the relevant factors and whether there has been a clear error of judgment. Overton Park, 401 U.S. at 416. However, "under this narrow scope of review, '[t]he court is not empowered to substitute its judgment for that of the agency.'" Bristol-Myers, 923 F. Supp. at 216 (quoting Overton Park, 401 U.S. at 416).

When reviewing an agency's construction of a statutory provision, a court's review is governed by the standard set forth in Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc., 467 U.S. 837 (1984). Under that framework, "[i]f the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." Chevron, 467 U.S. at 842-843 ("Chevron step

1"). On the other hand, if Congress has not directly addressed the issue or has done so ambiguously, the court may not "simply impose its own construction on the statute," but rather must determine whether the agency's construction is based on a permissible interpretation of the statute. Id. at 843 ("Chevron step 2"). See also id. at 843-45; Barnhart v. Walton, 535 U.S. 212, 217-18 (2002); United States v. Mead Corp., 533 U.S. 218, 229 (2001).

Deference to the agency under Chevron step 2 applies where, as here, "Congress delegated authority to the agency generally to make rules carrying the force of law," and especially where the agency's interpretation involves a "highly detailed" regulatory scheme to which the agency has brought its "specialized experience" to bear. Mead, 533 U.S. at 226, 235. Because Congress delegated to FDA the "authority to promulgate regulations for the efficient enforcement of" the FDCA, 21 U.S.C. 371(a), and specifically authorized FDA to engage in notice-and-comment rulemaking "necessary for the administration of [the Hatch-Waxman Amendments]," see 21 U.S.C. § 355 note, Pub. L. No. 98-417 § 105, 98 Stat. 1585, 1597 (1984), FDA's statutory interpretations and its regulations implementing the Hatch-Waxman Amendments are entitled to deference. See Apotex, Inc. v. Thompson, __ F.3d __, 2003 WL 22427772 (Fed. Cir. Oct. 27, 2003) ("Deference is due to an administrative agency's regulations particularly when the subject matter of the regulatory authority is a 'highly detailed' regulatory program to which the agency has brought its 'specialized expertise', . . . a characterization that aptly describes the FDA's role in the context of the regulatory scheme created pursuant to the Hatch-Waxman Act.") (quoting Mead, 533 U.S. at 235).

In addition, where a court is evaluating an agency's interpretation of its own regulations, the agency is entitled to "substantial deference." Thomas Jefferson Univ. v. Shalala, 512 U.S. 504, 512 (1994); United States Air Tour Ass'n v. FAA, 298 F.3d 997, 1005 (D.C. Cir. 2002)

(courts "defer to an agency's reading of its own regulation, unless that reading is plainly erroneous or inconsistent with the regulation") (internal citations omitted); Wyoming Outdoor Council v. U.S. Forest Service, 165 F.3d 43, 52 (D.C. Cir. 1999) (agency's construction of own regulation is controlling unless plainly erroneous or inconsistent with regulation); Bristol-Myers, 923 F. Supp. at 216 (court must be "especially deferential" of agency interpretation of own regulations).

In awarding IVAX exclusivity over Purepac in this case, FDA applied the plain language of the statute, which explicitly requires simultaneous notification upon the submission of an ANDA amendment containing a new paragraph IV certification. 21 U.S.C. § 355(j)(2)(B)(iii). To the extent the statute does not specifically address the consequences of an applicant's failure to comply with the simultaneous notice requirement, FDA "reasonably filled in a textual gap" by delaying the effective date of the submission of Purepac's ANDA amendment submission until notification was effected and the statutory requirements were thus fulfilled – something the agency had "considerable flexibility" to do. TorPharm, 260 F. Supp. 2d at 71, 80 (because statute is silent on issue of what follows from applicant's failure to follow "mandate of simultaneity," FDA had "considerable flexibility in deciding what the appropriate consequence of such a violation should be"); see also Niagara Mohawk Power Corp. v. FPC, 379 F.2d 153, 159 (D.C. Cir. 1967) (breadth of agency's discretion is at "zenith" when action assailed relates primarily to fashioning of policies, remedies and sanctions).

Thus, contrary to Purepac's claim (Brf. at 10-11), FDA's decision in this case is entitled to Chevron deference.[5] See Chevron, 467 U.S. at 843-44 & n.11 (1984) (in case of ambiguity,

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[5] Purepac relies on Christiansen v. Harris County, 529 U.S. 576 (2000), to argue that any FDA determination not embodied in rulemaking or formal adjudication is not entitled to Chevron deference. Br. at 10. That position was explicitly rejected by the Supreme Court in Barnhart:

court must uphold agency's interpretation if construction is permissible under the statute; court need not conclude that agency construction was only one it permissibly could have adopted or even reading court would have reached); see also Trans Union LLC v. FTC., 295 F.3d 42, 50 (D.C. Cir. 2002) ("Where Congress enacts an ambiguous provision within a statute entrusted to the agency's expertise, it has implicitly delegated to the agency the power to fill those gaps.") (citations and quotation marks omitted).

B. FDA's Determination That IVAX Is Entitled to Exclusivity on the '521 Patent Is Consistent With the Statute And the Regulations

FDA properly determined that IVAX is entitled to exclusivity on the '521 patent. The facts regarding timing are undisputed. Purepac filed its ANDA amendment containing a paragraph IV certification with FDA on November 20, 2002. However, Purepac did not immediately provide notice of the filing of the ANDA to the patent owner and the NDA holder for the listed drug, as required by 21 U.S.C. § 355(j)(2)(B)(iii). Instead, it waited until November 27, 2002, to send notice. In the meantime, IVAX submitted its original ANDA containing a paragraph IV certification on November 26, 2002, and FDA later determined that

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"[T]he fact that the Agency previously reached its interpretation through means less formal than 'notice and comment' rulemaking . . . does not automatically deprive that interpretation of the judicial deference otherwise its due. If this Court's opinion in Christensen v. Harris County suggested an absolute rule to the contrary, our later opinion in United States v. Mead Corp. denied the suggestion. Indeed, Mead pointed to instances in which the Court has applied Chevron deference to agency interpretations that did not emerge out of notice-and-comment rulemaking." 535 U.S. at 221 (citations omitted). Nevertheless, even if FDA's decisions here were not entitled to Chevron deference, FDA would still be entitled to deference under Skidmore v. Swift & Co., 323 U.S. 134, 139-40 (1944), under which courts give "considerable and in some cases decisive weight" to statutory interpretations "made in pursuance of official duty, [and] based upon more specialized experience and broader investigations and information" than a court is likely to have, provided that the administrative decision is carefully and thoughtfully made. The agency decisions challenged in this case "claim the merit of [their writers'] thoroughness, logic and expertness," and, as such, are at a minimum entitled to deference under Skidmore. Mead, 533 U.S. at 235.

submission was substantially complete. Under the FDCA and FDA regulations, IVAX was not required to provide notice at that time. Thus, IVAX's paragraph IV certification was effectively submitted before Purepac's.

1. A Paragraph IV Certification Contained in an ANDA Amendment is Ineffective Until Notice Is Provided

The requirements for an ANDA submission are set forth in 21 U.S.C. § 355(j)(2). That section requires, among other things, information on the similarity between the proposed ANDA drug and the listed drug approved under the NDA, bioequivalence data, proposed labeling, statements regarding components and composition of the drug, information on the manufacturing facility, patent certifications, and notice of paragraph IV certifications. The section specifies moreover that, for an ANDA amendment, notice of a paragraph IV certification must be given to the patent owner and NDA holder contemporaneously with its submission to FDA. See 21 U.S.C. § 355(j)(2)(B)(iii) ("if an application is amended to include a [paragraph IV certification], the notice required by clause (ii) shall be given when the amended application is submitted.") (emphasis added). FDA regulations contain the same requirement, and further emphasize the contemporaneous timing. 21 C.F.R. § 314.95(d) ("If an abbreviated application is amended to include [a paragraph IV certification], the applicant shall send the notice required by paragraph (a) of this section at the same time that the amendment to the abbreviated application is submitted to FDA.") (emphasis added).

The exclusivity provision, which appears later in the same subsection, grants exclusivity to the "first" paragraph IV filer by blocking the approval of later-filed ANDAs for 180 days when a "previous application has been submitted under this subsection." 21 U.S.C. § 355(j)(5)(B)(iv). The phrase "submitted under this subsection" refers to the submission of ANDA applications under 21 U.S.C. § 355(j) generally, and subsection 355(j)(2) specifically

which, as noted above, sets forth the necessary contents of such an application as well as the requirement that notice of any paragraph IV certifications be given to the patent owner and NDA holder.[6]

Thus, notice and exclusivity are interrelated under the statute, and an ANDA applicant must abide by the statute's notice requirements just as it must meet all the other requirements of 21 U.S.C. § 355(j)(2) in order for its ANDA to be considered for approval and exclusivity. Moreover, although an applicant submitting an initial ANDA must wait until FDA accepts the application before providing notice of any paragraph IV certifications contained in the application, when an ANDA is amended to include a new paragraph IV certification, the statute and regulations specifically require that such notice be given at the same time the ANDA amendment is submitted to FDA. Thus, simultaneous notice is an explicit statutory prerequisite for effective submission of an ANDA amendment containing a paragraph IV certification. 21 U.S.C. § 355(j)(2)(B)(iii).

a. The *TorPharm* Decision Upheld FDA's Position That Submission of an ANDA Amendment Containing a Paragraph IV Certification Is Incomplete Until Notice is Given

Judge Huvelle of this Court recently had occasion to examine the role of notice in the context of exclusivity determinations in a matter involving the approval of generic gabapentin (brand-name Neurontin). In a thorough and well-reasoned opinion, the court determined that the

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[6] Just as an ANDA applicant cannot submit an inadequate or sham application or amendment and expect its ANDA to qualify as a "previous application" under the exclusivity provision, see 21 C.F.R. § 314.107(c)(2) (requiring that ANDA be "substantially complete" in order to be eligible for exclusivity), neither can such an applicant ignore the critical notice requirements of subsection 355(j)(2)(B). Notice, as a practical matter, sets the Hatch-Waxman exclusivity scenario in motion by starting the clock on the patent owner's 45-day window to bring an infringement suit against the generic manufacturer, a process that, in turn, determines when, and whether, an ANDA can be approved and exclusivity awarded.

effect of an applicant's failure to give simultaneous notice of a paragraph IV certification in an amended ANDA would be to consider the ANDA effectively submitted as of the date that the required notice was ultimately provided. See TorPharm, 260 F. Supp. 2d at 71, 79-81. In that case, FDA received Purepac's gabapentin ANDA amendment with a paragraph IV certification to the patent in question on May 26, 2000. AR, Tab 15 at 6. Purepac sent notice of the certification to the NDA holder and the patent owner on June 13, 2000. Id. A competing generic manufacturer, TorPharm, Inc., also submitted an ANDA amendment containing a paragraph IV certification to the patent, which was mailed to FDA on June 13, 2000, and received on June 16, 2000. Id. at 7. TorPharm sent notice of the paragraph IV by letter dated June 12, 2000, which was mailed on June 13, 2000. Id.

TorPharm argued that Purepac's delay of several weeks in providing notice to the NDA holder meant that Purepac had failed to satisfy the statutory requirement of simultaneous notice. Specifically, because the statute provides that notice shall be given "when the amended application is submitted," 21 U.S.C. § 355(j)(2)(B)(iii), and FDA's regulation provides that the applicant shall send the notice "at the same time" that the ANDA amendment is submitted to FDA, 21 C.F.R. § 314.95(d), TorPharm argued that FDA should have found that Purepac's paragraph IV certification to the '482 patent was submitted prematurely and was therefore a nullity. AR, Tab 15 at 7; TorPharm, 260 F. Supp. 2d at 80. In such event, TorPharm's submission would have been the "first" effective paragraph IV certification, because TorPharm was the first applicant to comply with the statute and regulation by submitting an amendment and sending notice at the same time.

Purepac argued (as here) that the simultaneous notice requirement was irrelevant to consideration of the effective date of the submission of its paragraph IV certification, and that

the exclusivity and notice provisions of the statute were separate provisions that must be considered in isolation from each other. TorPharm, 260 F. Supp. 2d at 82 n.14. Purepac further contended that the two and one-half week delay between the time it filed its ANDA amendment and sent notice to the NDA holder and patent owner should be ignored because it was a reasonable period for preparing and sending the detailed statement of factual and legal basis required by the statute. AR, Tab 15 at 7; TorPharm, 260 F. Supp. 2d at 80 n.12.[7] Purepac thus argued that the date of its ANDA amendment alone (May 26, 2000) should govern for exclusivity purposes, irrespective of its delay in sending notice.

FDA rejected both analyses. AR, Tab 15 at 5-7. FDA agreed with TorPharm that both the statute and FDA regulations call for notice to be given contemporaneously with the submission of an ANDA amendment containing a paragraph IV certification. But neither the statute nor the regulations specify the consequences when an applicant provides delayed notice; nor do they compel the draconian conclusion that an applicant who fails to provide notice simultaneously should be disqualified altogether. FDA determined instead that Purepac's paragraph IV certification would be considered effectively submitted as of the date Purepac satisfied both statutory requirements of submission to FDA and notice to the patent holder. Because that date preceded the date by which TorPharm had both submitted its paragraph IV certification to FDA and provided notice, Purepac was the first ANDA applicant to meet the statutory requirements. FDA's determination that Purepac's submission would not be disqualified entirely, but merely deemed incomplete until notice was provided and the statutory

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[7] Under the statute, an ANDA applicant must notify the NDA holder and patent owner not only that an ANDA with a paragraph IV certification has been submitted but must also explain in detail the factual and legal basis for the applicant's opinion that the patent is invalid or not infringed. 21 U.S.C. § 355(j)(2)(B)(ii); 21 C.F.R. § 314.95(c).

requirements fulfilled, therefore struck a reasonable balance – neither rewarding Purepac for submitting its certification prematurely, nor unduly penalizing it by voiding its submission entirely.[8]

Judge Huvelle agreed. 260 F. Supp. 2d at 79-82. The court recognized that Purepac "did not strictly abide by the terms of the statutory provision . . . or the FDA regulation [requiring simultaneous notice]." Id. at 79-80. However, the court explained that, because the FDCA does not state the consequences of failure to "follow the mandate of simultaneity," FDA "had considerable flexibility in deciding what the appropriate consequence of such violation should be" and that the "choice of sanction [was] the agency's to make." Id. at 80-81. The court concluded that the agency "exercised that discretion reasonably" in its decision to delay the effective date of Purepac's ANDA amendment submission until such time as the requisite notice was provided – the same approach FDA followed in the case at bar. Id.[9] As the court explained:

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[8] FDA thus rejected Purepac's argument that the notice requirement should be ignored, as well as its claim that it substantially complied with the notice requirement because ANDA applicants needed a reasonable period of time to prepare their notices. As FDA pointed out, the statute contemplates that an ANDA applicant will have determined whether or not its product infringes a listed patent before it submits a paragraph IV certification to the patent, since that analysis is the basis for the certification itself. AR, Tab 15 at 7.

[9] The court flatly rejected Purepac's argument that its delay in providing notice should be ignored because it had substantially complied with the notice provision. 260 F. Supp. 2d at 80 n.12. However, because the court approved FDA's middle-ground approach, and because Purepac prevailed under that approach, the court found that it "need not address" Purepac's argument that the notice provision is entirely irrelevant to exclusivity. Id. at 82 n.14. Nevertheless, the court implicitly rejected any such claim by virtue of its ruling that: (1) Purepac violated the simultaneous notice provision; (2) FDA had considerable flexibility in fashioning an appropriate remedy for the violation; and (3) FDA had exercised its discretion reasonably in determining that Purepac's ANDA amendment was not effectively submitted until it provided notice. In light of these findings, Purepac's contention in this case – that FDA is prohibited from considering an applicant's late notice in awarding exclusivity – cannot be reconciled with TorPharm.

> [T]he agency determined that where a certification is submitted without simultaneous notice, that certification does not become effective for exclusivity purposes until the notice is actually sent. In other words, where notice is provided after the certification is received, the agency's policy constructively moves the certification's "submission" date to the day on which the applicant mailed the notice. This approach . . . acknowledges that notice and certification must occur together, and therefore refuses to give legal recognition to one act until the other has been effectuated as well. As such the agency's policy . . . punishes an applicant's failure to furnish simultaneous notice by refusing to make its solitary certification immediately effective upon receipt by the agency. Those who heed the notice provision reap the benefit of instant acceptance; those who do not, do not.

Id.

In this case, as in TorPharm, Purepac failed to heed the statutory requirement of simultaneous notice and may not therefore "reap the benefit" of instant acceptance of its ANDA amendment. As in TorPharm, FDA determined that Purepac's paragraph IV certification would not be disqualified entirely, but would not be considered effectively submitted until the date Purepac provided notice to the NDA holder and patent holder and therefore fulfilled the statutory requirements. However, unlike TorPharm, where the application of these rules led to the conclusion that Purepac was "first" and eligible for 180-day exclusivity, Purepac lost the battle of effective submission dates in this case and, with it, its claim to 180-day exclusivity for generic metformin.

b. FDA Has Not Imposed Additional Conditions For Exclusivity

In light of the above, Purepac's claim that FDA has improperly imposed an additional requirement for exclusivity is unpersuasive. Purepac contends that Congress set forth only a "single criterion" for exclusivity – that the ANDA filer be "the first filer to submit a Paragraph IV certification to FDA" (Brf. at 11) – and that the agency's action in this case "improperly adds a condition to obtaining exclusivity beyond those enunciated by Congress." Brf. at 14. Purepac's argument, however, begs the question of what constitutes a proper "submission" of a

paragraph IV certification. Rather than imposing a new condition precedent to obtaining exclusivity, FDA's statutory construction merely assures that the conditions already set forth in the statute are satisfied by refusing to consider an ANDA amendment to be effectively "submitted" unless and until the applicant has satisfied all of the statutory requirements pertaining to such a submission. For ANDA amendments, the statute requires that notice be given contemporaneously with submission of the amendment to FDA, and FDA has reasonably concluded that an amendment will not be considered effectively submitted until the requisite notice is given.

Thus, contrary to Purepac's claim, FDA has in no sense added a new or additional requirement for obtaining exclusivity. The fact that the exclusivity provision itself does not explicitly refer to notice, does not mean that the notice requirement is immaterial to the exclusivity calculus. To the contrary, providing notice of a paragraph IV certification is an essential component of the ANDA submission process, and the particulars of who must receive notice, what the notice must contain, and when it must be given, are fully detailed alongside the other statutory requirements for ANDA submissions. See 21 U.S.C. § 355(j)(2)(B)(i), (ii) & (iii). As such, notice (and the content and timing thereof) may properly be taken into account by FDA in making exclusivity determinations under the statute.[10]

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[10] Nor is FDA's approach "squarely contradicted" by its own regulations as Purepac contends. Brf. at 9. Purepac correctly points out that FDA's exclusivity regulations refer to the first applicant "that submits an application that is both substantially complete and contains a [paragraph IV certification]." 21 C.F.R. § 314.107(c)(2); Brf. at 12. However, Purepac misconstrues this regulation when it asserts that "[t]here is only one requirement for an application to be substantially complete" – namely that it contain the results of any required bioequivalence studies or a request for a waiver thereof. Brf. at 12. Although the regulation does indeed mandate that a "substantially complete" ANDA application "must contain" such bioequivalence data, nothing in the regulation suggests that this is the sole requirement for substantial completeness. Indeed, such a reading would be absurd, as even Purepac appears to recognize in a footnote. Brf. at 12 n.1 (explaining that "substantially complete" requirement

c. Notice and Exclusivity are Complementary Elements of the Statutory Scheme and Cannot be Viewed in Isolation

Purepac further argues that notification "is not relevant to the award of exclusivity" and that FDA "mistakenly grafted the notification provision of the FDCA onto the very different exclusivity provision." Brf. at 13, 16. Purepac thus contends that, because notification and exclusivity "were enacted to serve different purposes" and reside in different subparts of the statute, FDA was forbidden from "import[ing]" the notice requirement into its exclusivity analysis. Id. at 15, 13-18. This argument is meritless.

Purepac's contention that notice and exclusivity "serve very distinct roles" (id. at 16) reflects an unrealistic and unduly narrow view of the overall statutory scheme. While it may be true that exclusivity benefits only the ANDA first-filer, the notification provision was not enacted solely to permit the brand name company to protect its patent rights. Notification sets in motion the whole process of patent litigation that enables a generic applicant to bring its product to market before the expiration of patent protection, and without the risk of damages inherent in a traditional patent infringement context. By making the act of submitting a paragraph IV certification to FDA an artificial act of infringement, Congress established a mechanism whereby the resolution of patent rights vis a vis generic and brand name manufacturers could be resolved in a relatively swift and straightforward fashion – thereby substantially speeding the path to generic drug approval and marketing. This mechanism, with its significant benefits, is

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insures that applicants file "a legitimate ANDA" in order to be eligible for exclusivity). By specifically identifying bioequivalence data as a mandatory part of a "substantially complete" ANDA, the regulation does not thereby waive the notice obligation or any of the other ANDA submission requirements set forth in the statute and regulations. Thus, Purepac's reliance on FDA's "substantial completeness" regulation is unavailing.

only activated when the ANDA applicant gives notice of its paragraph IV certification to the NDA holder and patent owner.

The provision of notice as required by the statute is particularly important in the context of exclusivity. As the Mova court recognized, 180-day exclusivity is a reward for the ANDA applicant exposing itself to the risk of patent litigation. 140 F.3d at 1064. It is the notice to the patent owner and NDA holder that precipitates such risk; the submission of a paragraph IV certification alone without the notice carries no risk. Thus, the purpose of the notice provision is much broader than Purepac suggests. Properly viewed, notice is a critical component of the overall Hatch-Waxman scheme.

Moreover, it is a fundamental tenet of statutory construction that courts (and agencies) must look to the statute as a whole rather than individual statutory provisions in isolation. "[T]o prevent statutory interpretation from degenerating into an exercise in solipsism, 'we must not be guided by a single sentence or member of a sentence, but look to the provisions of the whole law.'" County of Los Angeles v. Shalala, 192 F.3d 1005, 1014 (D.C. Cir. 1999) (quoting United States Nat'l Bank v. Independent Ins. Agents of Am., Inc., 508 U.S. 439, 455(1993)); accord Pilot Life Ins. Co. v. Dedeaux, 481 U.S. 41, 51 (1987) ("In expounding a statute, we must not be guided by a single sentence or member of a sentence, but look to the provisions of the whole law, and to its object and policy.") (internal quotes omitted); McCarthy v. Bronson, 500 U.S. 136, 139 (1991) (agreeing that, read in isolation, petitioner's reading was the most natural one but stating that "statutory language must always be read in its proper context"); Massachusetts v. Morash, 490 U.S. 107, 115 (1989); Offshore Logistics, Inc. v. Tallentire, 477 U.S. 207, 221 (1986); Mastro Plastics Corp. v. NLRB, 350 U.S. 270, 285 (1956) (rejecting literal interpretation of words in "complete isolation from their context in the Act"); Eldred v. Ashcroft, 255 F.3d

849, 854 (D.C. Cir. 2001) (Sentelle, J., dissenting) ("it is a 'cardinal rule of construction' that 'the whole law is to be taken together, and one part expounded by any other which may indicate the meaning annexed . . . to ambiguous phrases'") (quoting Postmaster-General v. Early, 25 U.S. (12 Wheat.) 136, 152, 6 L.Ed. 577 (1827)).

Even under a Chevron step 1 analysis, courts look to the statute as a whole to understand the plain meaning of an individual provision. As the D.C. Circuit explained:

> Under Chevron step one, "we consider not only the language of the particular statutory provision under scrutiny, but also the structure and context of the statutory scheme of which it is a part." Illinois Pub. Tele. Ass'n v. FCC, 117 F.3d 555, 568 (D.C. Cir.), modified, 123 F.3d 693 (1997), cert. denied, 523 U.S. 1046, 118 S. Ct. 1361, 140 L. Ed.2d 511 (1998); accord Conroy v. Aniskoff, 507 U.S. 511, 515, 113 S. Ct. 1562, 123 L. Ed.2d 229 (1993) ("[T]he meaning of statutory language, plain or not, depends on context."); Davis v. Michigan Dep't of Treasury, 489 U.S. 803, 809, 109 S. Ct. 1500, 103 L. Ed.2d 891 (1989) ("[W]ords of a statute must be read in their context and with a view to their place in the overall statutory scheme.").

County of Los Angeles, 192 F.3d at 1014. Thus, contrary to Purepac's contention, FDA properly considered the exclusivity and notice provisions in the context of the overall Hatch-Waxman scheme.

In light of the above, Purepac's reliance on Indiana Michigan Power Co. v. Dep't of Energy, 88 F.3d 1272 (D.C. Cir. 1996) is misplaced. Pl. Brf. at 15-16. Although the court determined in that case that two particular requirements of the Nuclear Waste Policy Act were independent, id. at 1276, all statutes are different, and the provisions of the Nuclear Waste Policy Act at issue in that case have no bearing on the proper interpretation of the FDCA.[11] Indeed, the

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[11] Similarly, in Newmark v. Principi, 283 F.3d 172, 178 (3d Cir. 2002), on which Purepac relies (Brf. at 16), the court concluded that two sections of the Equal Access to Justice Act ("EAJA") provided for two separate types of attorney fees awards. That court's construction of the EAJA likewise has no bearing here. Purepac also asserts that FDA's decision in this matter conflicts with a previous position taken by the agency in the course of litigating American Bioscience, Inc. v. Shalala, 142 F. Supp. 2d 1 (D.D.C. 2000), rev'd on other grounds, 243 F.3d 579 (D.C.

Indiana Michigan Power court also recognized, consistent with the cases cited above, that "we must interpret the section in light of the whole statutory scheme." Id. at 1275. In any event, for every case finding particular statutory provisions unrelated, there are just as many or more cases finding statutory provisions interrelated. See, e.g., Fort Ord Toxics Project, Inc. v. California EPA,189 F.3d 828, 832 (9th Cir. 1999) ("In this case, plaintiffs' attempt to limit § 113(b) more narrowly than § 113(h) is inconsistent with the broad language used in § 113(b) and would hinder the clear purpose of § 113(h). . . . This being the case, we must read § 113(h) in accordance with the broad language of § 113(b) in order to effectuate congressional intent.").

In this case, FDA has not "grafted" one provision of the Hatch-Waxman Amendments onto a "very different" second provision. Brf. at 16. To the contrary, as noted above, the notice and exclusivity provisions are related parts of 21 U.S.C. § 355(j), and can only be properly understood in the context of the ANDA approval scheme as a whole. Indeed, the statutory requirements for ANDA submissions set forth in 21 U.S.C. § 355(j)(2) expressly include simultaneous notice for a paragraph IV certification in an ANDA amendment, 21 U.S.C. § 355(j)(2)(B)(iii), and a statement that notice will be given in the future for a paragraph IV certification in an original ANDA submission, 21 U.S.C. § 355(j)(2)(B)(i). Exclusivity under the statute is not granted to any ANDA submission that is first in time regardless of how far it deviates from the submission requirements of section 355(j)(2). Instead, the phrase "submitted under this subsection" in section 355(j)(5)(B)(iv) necessarily refers to an application or

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Cir. 2001), a case involving the approval of an ANDA submitted by Baker Norton Pharmaceuticals. See Pl. Brf. at 17-18. The argument that Purepac references, however, was made in the context of FDA's late listing regulation, 21 C.F.R. § 314.94(a)(12)(vi), a regulation and context not at issue here.

amendment submitted pursuant to the provisions of section 355(j)(2) – which includes the essential requirement of notice.

Thus, FDA properly determined that Purepac's ANDA amendment containing a certification to the '521 patent was not effectively submitted to FDA until November 27, 2002 – the date Purepac sent notice to BMS.

2. The Effective Date of the Submission of an Original ANDA Is Determined by the Date the Application is Substantially Complete

Purepac next argues that, even if the timing of notification is relevant to the determination of exclusivity, Purepac provided notice of its paragraph IV certification to BMS before IVAX did. Purepac contends that FDA's award of exclusivity to IVAX was therefore arbitrary and capricious because it reflects "disparate treatment between new and amended filers." Brf. at 19. Because, in Purepac's view, "there is no relevant difference between a new ANDA and an amended ANDA, there is no possible justification for FDA to establish different requirements for amended and new ANDA filers to qualify for exclusivity." Id. at 20.

Purepac's argument is unavailing, however, for the simple reason that it ignores the statutory language, which itself treats the notice requirement differently for original ANDAs and ANDA amendments. For an original ANDA, there is no statutory requirement that the applicant provide notice to the NDA and patent holder at the same time as the ANDA submission. Instead, the statute states that notice should be provided in the future: that the applicant submitting a certification with an original ANDA "shall include in the application a statement that the applicant will give the notice required by clause (ii) . . . ." 21 U.S.C. § 355(j)(2)(B)(i) (emphasis added). The statute is otherwise silent as to when that notice should be given. This stands in stark contrast to the statutory provision governing ANDA amendments, which specifies

that notice "shall be given when the amended application is submitted." 21 U.S.C. § 355(j)(2)(B)(iii).

FDA's regulations echo this distinction. The regulations provide that an applicant submitting an original ANDA with a paragraph IV certification should wait to provide notice to the NDA and patent holder until FDA has acknowledged that the ANDA has been received and is sufficiently complete to permit a substantive review. See 21 C.F.R. § 314.95(b). Otherwise, ANDA applicants would provide notice of paragraph IV certifications that FDA may never accept for filing.[12] For original ANDAs, therefore, the regulations require that notice be provided "when [the applicant] receives from FDA an acknowledgment letter . . . ." 21 C.F.R. § 314.95(b). Moreover, if, after completion of its threshold review, FDA determines that the original ANDA was substantially complete when first received, FDA considers the ANDA to have been effectively received on the date the substantially complete application was date-stamped by FDA, not the date that FDA completes its threshold review. See 21 C.F.R. § 314.101(b); see also 54 Fed. Reg. at 28889. For ANDA amendments, however, notice is to be provided "at the same time that the amendment to the abbreviated application is submitted to FDA." 21 C.F.R. § 314.95(d).

Thus, unlike ANDA amendments, the date of notice is not a factor in determining the effective date of an original ANDA's submission to FDA. Indeed, if the date of notice were

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[12] Because notice of a paragraph IV certification allows the patent owner and NDA holder to sue the ANDA applicant for patent infringement, premature notification of a paragraph IV certification in an application that is not accepted for filing could generate unnecessary patent litigation. As FDA explained in proposing the above regulation, "The statute and legislative history of Title I demonstrate that Congress did not intend incomplete application submissions to trigger legal action by a patent owner or approved application holder. The agency therefore proposes that the notice be sent only upon submission of a 'complete' application." 54 Fed. Reg. at 28887.

taken into account, the applicant would be disadvantaged by actions not within its control. Because a manufacturer submitting an original ANDA must wait for FDA to complete its threshold review of the application and then send an acknowledgment letter by regular mail, it would be unfair to delay the effective filing date of the ANDA by weeks or months solely on account of FDA's review and mailing time. By contrast, FDA does not send acknowledgment letters for ANDA amendments. As there is no FDA review time that delays official acceptance of the amendment, there is no justification for delaying notice to the patent owner and NDA holder.

Purepac's claim that FDA had "no possible justification" for applying different requirements to original ANDAs and ANDA amendments is thus unfounded. As the above makes clear, FDA had ample and compelling reasons for treating Purepac's and IVAX's submissions differently. Not least of these are the fact that: (1) the language of the statute governing the two submissions is different, and, in particular, contains different notice requirements; (2) the language of the applicable regulations is different; and (3) there are policy reasons for treating the two situations differently, namely avoiding unnecessary patent litigation and not penalizing original ANDA applicants for the time it takes FDA to conduct its threshold review and for the acknowledgment letter to arrive in the mail.

Thus, FDA reasonably interpreted the statute and regulations to determine that the effective date of an original ANDA is the date a substantially complete ANDA is received by the agency. The date on which the applicant provides notice to the NDA holder and patent owner is not part of the calculation. Thus, while the effective date of Purepac's amended ANDA submission is November 27, 2002 (the date Purepac provided notice of its paragraph IV

certification to BMS), the effective date of IVAX's ANDA submission is November 26, 2002 (the date the application was received by FDA).

3. The Date IVAX Provided Notice is Irrelevant to the Analysis

Finally, Purepac argues that FDA must take into account the date IVAX sent notice of its paragraph IV certification to BMS and "penalize" IVAX for failing to notify BMS promptly upon receipt of FDA's acknowledgment letter. FDA mailed its acknowledgment letter to IVAX on January 14, 2003, stating that the application was acceptable for filing. Although there is no evidence in the record as to precisely when IVAX received the January 14, 2003 letter, IVAX sent notice to BMS on February 3, 2003. Because the regulations require original ANDA applicants to provide notice of paragraph IV certifications contained in the application "when [the applicant] receives from FDA an acknowledgment letter stating that its [ANDA] is sufficiently complete to permit a substantive review," 21 C.F.R. § 314.95(b), Purepac asserts that IVAX's notice was untimely and that the effective date of IVAX's ANDA submission should therefore be delayed, as Purepac's was, to February 3, 2003, the date IVAX sent its notification to BMS. Brf. at 22-24. FDA disagrees for several reasons.[13]

First, as noted above, nothing in the statute specifies the required timing for an original ANDA applicant to submit notice. Thus, IVAX's delay does not violate any explicit provision of the statute. In contrast, the statute expressly requires an applicant submitting an ANDA amendment to provide notice "when the amended application is submitted." Thus, Purepac's delay in sending notice to BMS indisputably violated the statute, while IVAX's delay did not.

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[13] Purepac trumpets the fact that it sent its notice letter to BMS "just two days after November 25, 2002, the day the FDA first made public that the '521 patent had listed in the Orange Book." Brf. at 22. As noted above, however, the patent was actually submitted for listing on November 20, 2002, and Purepac began sending paragraph IV certifications to FDA on November 5, 2002 – more than three weeks before it first sent notice to BMS. AR, Tab 4.

Second, contrary to Purepac's arguments, the TorPharm decision does not mandate that the date IVAX provided notice be considered in the effective date calculation. Rather, the court in TorPharm recognized that neither the statute nor the regulation specifies the consequences of late notice when an amended ANDA is submitted. Likewise, with respect to an original ANDA application, nothing in the regulation specifies the consequences of less than timely notice (and the statute does not even indicate when notice is required). However, because the delay in notice for an original ANDA is caused in the first instance by FDA's threshold review of the ANDA application, FDA has reasonably concluded that the date of notice is not part of the calculation of the effective submission date of the original ANDA. That is a matter properly within the agency's discretion.

Third, as Purepac points out, FDA's regulation requires notice for an original ANDA "when [the applicant] receives from FDA an acknowledgment letter." 21 C.F.R. § 314.95(b). However, the exact timing of "when" in this context is not clear – whether it is the same day or the next day or shortly thereafter – because the applicant's act must follow an event by another actor outside of its control, namely the mailing and receipt of FDA acknowledgment letter. By contrast, the statutory requirement for providing notice in connection with an ANDA amendment – "the notice . . . shall be given when the amended application is submitted," 21 U.S.C. § 355(j)(2)(B)(iii) – refers to two acts by the same actor that can be completed simultaneously. Moreover, FDA's regulation with respect to ANDA amendments, unlike its counterpart for original ANDAs, contains language that unambiguously requires immediate action: it requires notice "at the same time that the amendment to the abbreviated applications is submitted to FDA." 21 C.F.R. § 314.95(d) (emphasis added).

For these reasons, and those explained in section I.B.2 above, FDA's calculation of the effective date of submission of an original ANDA, unlike an amended ANDA, does not include the date notice was provided. Because FDA considers IVAX's substantially complete ANDA to have been submitted as of the date it was received by the agency, it is irrelevant for purposes of exclusivity precisely when IVAX provided notice to BMS, so long as such notice was in fact provided. Unlike ANDA amendments, neither the statute nor FDA regulations require simultaneity for notice of paragraph IV certifications contained in original ANDAs. As such, the date of notice plays no role in calculating the date of ANDA submission and is thus not part of the exclusivity analysis.[14]

* * *

Accordingly, for the reasons set forth above, FDA's exclusivity determination with respect to the '521 patent was not arbitrary, capricious or contrary to law, and should be upheld.

II. PUREPAC HAS NOT SHOWN IT WILL SUFFER IRREPARABLE INJURY ABSENT THE REQUESTED PRELIMINARY INJUNCTION

"The *sine qua non* of granting any preliminary injunctive relief is a clear and convincing showing of irreparable injury to the plaintiff." Experience Works, Inc. v. Chao, 267 F. Supp. 2d 93, 96 (D.D.C. 2003). Because Purepac's likelihood of success is extremely slim, it "would have to make a very substantial showing of severe irreparable injury" in order to prevail on its motion. National Pharm. Alliance v. Henney, 47 F. Supp. 2d 37, 41 (D.D.C. 1999). Irreparable injury is a "very high standard." See Varicon Int'l v. Office of Personnel Mgmt., 934 F. Supp. 440, 447 (D.D.C. 1996); Bristol-Myers, 923 F. Supp at 220. The injury alleged must be certain, great,

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[14] Whether it would be appropriate for FDA to impose some other form of sanction or regulatory consequence in a case where an ANDA applicant (unlike IVAX here) unreasonably delays sending notice after receipt of FDA's acknowledgment letter is not at issue here and is, in any event, a matter within the agency's discretion.

actual, and imminent, Wisconsin Gas Co. v. FERC, 758 F.2d 669, 674 (D.C. Cir. 1985), and it must be "more than simply irretrievable; it must also be serious in terms of its effect on the plaintiff." Mylan v. Thompson, 139 F. Supp. 2d at 27 (quoting Gulf Oil Corp. v. Dep't of Energy, 514 F. Supp. 1019, 1026 (D.D.C. 1981)).

It is well settled that mere economic loss in and of itself does not constitute irreparable harm. Wisconsin Gas, 758 F.2d at 674; Mylan v. Shalala, 81 F. Supp. 2d. at 42; Bristol-Myers, 923 F. Supp. at 220 (D.D.C. 1996). "Mere injuries, however substantial in terms of money, time and energy expended" are inadequate. Wisconsin Gas, 758 F.2d at 674 (quoting Virginia Petroleum Jobbers Ass'n v. FPC, 259 F.2d 921, 925 (D.C. Cir. 1958)). Even irrecoverable economic loss does not rise to the level of irreparable harm unless the financial injury is so great as to "cause extreme hardship to the business, or even threaten destruction of the business." Gulf Oil, 514 F. Supp. at 1025; see also Wisconsin Gas, 758 F.2d at 674 (recoverable monetary loss may constitute irreparable harm only where it "threatens the very existence of the movant's business"); Experience Works, 267 F. Supp. 2d at 96 (a $21.1 million reduction in funding is a serious financial blow, but one frequently faced by other similar entities, and is not an economic loss that threatens the survival of the business); Sociedad Anomia Vina Santa Rita v. Dep't of Treasury, 193 F. Supp. 2d 6, 14 (D.D.C. 2001) ("financial harm alone cannot constitute irreparable injury unless it threatens the very existence of the movant's business").

The cases Purepac cites, Brf. at 24-26 & n.4, contain only a cursory analysis of the economic harm element, and, with one exception, do not mention, discuss, or distinguish Wisconsin Gas or Gulf Oil or any of the other cases cited above on economic harm.[15] However,

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[15] See Mova, 140 F.3d at 1066 n.6; CollaGenex Pharm., Inc. v. Thompson, 2003 WL 21697344 (D.D.C. July 22, 2003); Pharmacia & UpJohn Co. v. Ranbaxy Pharm., Inc., 274 F. Supp. 2d 597, 614 (D.N.J. 2003); Mova Pharm. Corp. v. Shalala, 955 F. Supp. 128, 131 (D.D.C. 1997); Bracco

Wisconsin Gas and Gulf Oil – holding that economic harm must be extreme to constitute irreparable injury – are still the leading cases in this Circuit, and they are currently being applied by the judges of this Court. See, e.g., Experience Works, Inc., 267 F. Supp. 2d at 96; Role Models America, Inc. v. White, 193 F. Supp. 2d 76, 86 (D.D.C. 2002), rev'd on other grounds, 317 F.3d 327 (D.C. Cir. 2003); Sociedad Anomia Vina Santa Rita v. Dep't of Treasury, 193 F. Supp. 2d at 14; LeBoeuf, Lamb, Greene & MacRae, LLP. v. Abraham, 180 F. Supp. 2d 65, 71-72 (D.D.C. 2001). Moreover, there are just as many courts that have addressed claims of anticipated monetary harm from competition in the pharmaceutical marketplace such as Purepac alleges it will suffer here, that have concluded that such claims are insufficient to demonstrate "irreparable injury" for purposes of preliminary injunctive relief. See, e.g., Mylan v. Thompson, 139 F. Supp. 2d at 26-28; Mylan v. Shalala, 81 F. Supp. 2d. at 42-43; Bristol-Myers, 923 F. Supp. at 220-21; Mead Johnson Pharm. Group v. Bowen, 655 F. Supp. 53, 56 (D.D.C. 1986), aff'd, 838 F.2d 1332 (D.C. Cir. 1988).

Notwithstanding this well-established doctrine, economic loss is precisely the type – and the only type – of harm that Purepac alleges it will suffer in the absence of an injunction. See Brf. at 26-30. Specifically, Purepac argues that, if it were awarded exclusivity, it would obtain a significant market share that would produce a profit of $30.1 to $45.7 million over the 180-day exclusivity period. Id. at 28. The loss of exclusivity would cause a 3-11% reduction in annual revenue for Purepac's parent company, Alpharma, Inc. Declaration of Robert P. Sanzen (Vice President for Sales and Marketing at Alpharma) ¶ 21; Brf. at 29 n.7. Such a loss of estimated

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Diagnostics, Inc. v. Shalala, 963 F. Supp. 20, 29 (D.D.C. 1997). The one exception in the cases cited by Purepac is TorPharm, Inc. v. Shalala, 1997 WL 33472411 (D.D.C. Sept.15, 1997). In TorPharm, the court found that projected losses of $200 million were sufficiently imminent, serious and irretrievable to meet the test of Wisconsin Gas and Gulf Oil.

future market share, however, is a far cry from the required demonstration of a "serious" and "irretrievable" loss that "would significantly damage its business above and beyond a simple diminution in profits." Mylan v. Thompson, 139 F. Supp. 2d at 27; Mylan v. Shalala, 81 F. Supp. 2d at 42. Furthermore, Purepac is by no means a one-product company. See Bracco Diagnostics, 963 F. Supp. at 29 (recognizing injury to one-product line company); CollaGenex, 2003 WL 21697344 (drug in question allegedly represented 80% of revenue). Purepac and Alpharma have over 200 products. Sanzen Decl. ¶ 7.

Purepac also alleges the "loss of the first-mover advantage" that has "enduring market share results." Brf. at 26-27. These alleged losses include "access to important customers," lost opportunity to increase sales over other products, unspecified long term purchasing agreements, and "residual market share benefits." Id. at 26. These are essentially different forms of economic loss that are even more speculative than Purepac's monetary allegations. Within the D.C. Circuit, courts "have generally been hesitant to award injunctive relief based on assertions about lost opportunities and market share." Mylan v. Shalala, 81 F. Supp. 2d at 42 (citing cases); see also Mylan v. Thompson, 139 F. Supp. 2d at 27 (same).

Because Purepac has not shown that it will suffer an "irretrievable" loss that "could significantly damage its business above and beyond a simple diminution in profits," its allegations fall well short of the showing necessary to support a finding of irreparable injury. Mylan v. Thompson, 139 F. Supp. 2d at 27; Mylan v. Shalala, 81 F. Supp. 2d at 42.

III. THE BALANCE OF HARMS AND THE PUBLIC INTEREST WEIGH AGAINST PUREPAC'S REQUEST FOR INJUNCTIVE RELIEF

Purepac has also failed to show that the harm it will purportedly suffer in the absence of injunctive relief outweighs the potential harm to other affected parties or that the entry of such relief would further the public interest. Serono Labs v. Shalala, 158 F.3d 1313, 1326 (D.C. Cir.

1998); Mylan v. Shalala, 81 F. Supp. 2d at 44-45. Although FDA has no commercial stake in the outcome of this litigation, FDA is the government agency charged with implementing the statutory scheme governing the approval of both pioneer and generic drugs and with ensuring that all marketed drugs are safe and effective. As such, FDA's interest coincides with that of the public.

The public benefits from the entry of lower cost drugs into the marketplace. IVAX has demonstrated that it is ready and able to market. However, an award of exclusivity to Purepac could hold up approvals of all generic metformin. Although Purepac's counsel stated at the TRO hearing that Purepac believed it was only "days away" from approval of its ANDA (Tr. at 27), nothing in Purepac's written submissions or otherwise in the record supports that assertion.[16] Moreover, as Purepac has acknowledged, there are other companies whose ANDAs for metformin have been tentatively approved by FDA. Sanzen Decl. ¶ 20. Thus, if Purepac is awarded exclusivity, and is unable or unwilling to go to market, all other metformin ANDAs will be blocked from gaining approval and going to market. Keeping lower-cost generic metformin off the market would be detrimental to the public interest.

Moreover, there is no public policy reason for Purepac to be awarded 180-day exclusivity. Its argument for first-submitter status is not based on any investments in developing its generic drug product faster than other companies. Instead, it out-gamed its competitors by submitting paragraph IV certifications before it was proper to do so, to make sure one of its

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[16] Because the status of an ANDA is considered confidential commercial information, such information may not be publicly disclosed without the company's permission. Accordingly, if the Court approves an *in camera* submission, FDA will provide a declaration from FDA's Office of Generic Drugs regarding the current status of Purepac's metformin ANDA and its prospects for imminent approval.

paragraph IV certifications was received on the same day FDA received the '521 patent, and before FDA's listing of that patent was public.

The public also benefits from FDA ensuring that generic drugs are approved in accordance with the statutory scheme that Congress enacted and that the rewards and incentives contained in the statute are properly allocated in the manner Congress intended. To that end, FDA established rules and policies that are applied to all ANDAs regardless of the specific circumstances. The preliminary injunctive relief sought by Purepac would upset the agency's careful interpretation of the statute and disrupt the agency's administration of the Hatch-Waxman procedures governing patent listings and certifications.

Under these circumstances, both the balance of harms and the public interest weigh against Purepac's request for preliminary injunctive relief.

CONCLUSION

For the foregoing reasons, Purepac's motion for preliminary injunction should be denied.

Respectfully submitted,

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